

## OPEN PEER REVIEW REPORT 2

**Name of journal:** Neural Regeneration Research

**Manuscript NO:** NRR-D-17-00739

**Title:** Hydrogen peroxide mediates pro-inflammatory cell-to-cell signaling: a new therapeutic target for inflammation?

**Reviewer:** Attila Köfalvi, University of Coimbra, Portugal.

### COMMENTS TO AUTHORS

The weaknesses are the high catalase concentrations required which question selectivity, the lack of statistical analyses and the stub shortness of the text, without any regular discussion.

This manuscript reports an interesting new method how H<sub>2</sub>O<sub>2</sub> may act as an extracellular mediator to promote NO release in macrophages, and to a lesser extent, TNF- $\alpha$  production. The manuscript's language is generally very good and neat, but the paper is unnecessarily short. There is no reason to reduce so drastically the Methods section. I believe that all papers should be a standalone work, intelligible in themselves. The Discussion is poor, it is practically similar to an Abstract. There are thousands of papers published on H<sub>2</sub>O<sub>2</sub> and inflammation. Discussing the known roles of H<sub>2</sub>O<sub>2</sub> in brain (patho)physiology and expanding the horizon over these new data would be certainly helpful. The authors chose Alzheimer's disease as a keyword but there is no special link to this disease (more than to any other). Actually, I know more studies with H<sub>2</sub>O<sub>2</sub> destroying mitochondria in striatal dopaminergic nerve terminals, with relevance to Parkinson's disease.

Please note that intercellular communication with H<sub>2</sub>O<sub>2</sub> has been already described in the brain (e.g. Sidló et al., *Neurochem Int.* 2008 Jan;52(1-2):80-8.)

My major issue here is that effects are not statistically compared to control, so we don't even know where we see significant inhibition by catalase.

My second issue is that catalase concentrations required for eliminating H<sub>2</sub>O<sub>2</sub> in these assays seem very high. As catalase is an efficient enzyme, it may mean eventually that the enzyme has to be first internalized in the macrophages, which is promoted by high catalase concentrations.

Minor:

Dose appears 7 times in the MS. As you work in vitro, you should prefer using the term concentration rather than dose.

Introduction, line 56: using quite three different pro-inflammatory activators - maybe ...three quite...